Mitochondrial Genome: Sequencing

Test Code: JD  
Turnaround time: 8 weeks  
CPT Codes: 81479 x1

**Condition Description**

Mitochondrial disorders are a frequent cause of genetic disease [1]. They comprise a clinically heterogeneous group of diseases caused by mutations of either nuclear or mitochondrial DNA (mtDNA) which may result in decreased cellular energy production due to a dysfunctional mitochondrial respiratory chain. This sequencing assay is available to detect mutations in the mtDNA genome. Mutations in nuclear genes with mitochondrial function will not be detected by this analysis.

Clinical presentation of mtDNA disorders is variable. Most involve multiple organ systems and frequently present with neurologic and myopathic symptoms, which may be intermittent, but disorders may be confined to one organ such as the eye in Leber hereditary optic neuropathy (LHON). Age of onset also varies though symptoms may frequently develop in childhood.

Common clinical features of mtDNA disorders include external ophthalmoplegia, ptosis, cardiomyopathy, diabetes mellitus, sensorineural deafness, optic atrophy, pigmentary retinopathy, myopathy and exercise intolerance [3]. The central nervous system findings are often seizures, dementia, migraine, stroke-like episodes, ataxia, spasticity and encephalopathy. However, due to a significant clinical variability, some individuals do not fit into a specific clinical diagnosis. Heteroplasmy, which is the uneven distribution of mtDNA molecules during cell division, may results in variable penetrance and severity of symptoms, depending on the level of mutant mitochondria [4].

Some discrete clinical syndromes are well established, for which targeted testing is available:

- Kearns-Sayre syndrome (KSS)
- Pearson syndrome
- Chronic progressive external ophthalmoplegia (CPEO)
- Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- Myoclonic epilepsy with ragged-red fibers (MERRF)
- Retinitis Pigmentosa and Ataxia (NARP)
- Leber hereditary optic neuropathy (LHON)
- Leigh syndrome (LS)

Sequence analysis of the entire mtDNA genome is available to test for mitochondrial mutations. This test is intended for patients with a diagnosis of a mitochondrial disorder. If applicable, testing for common mutations associated with specific mitochondrial disorders should be performed first. Low levels of heteroplasmy may not be detected.

References:

**Indications**

This test is indicated for:

- Individual with a clinical diagnosis of a mitochondrial DNA disorder

**Methodology**

The entire mitochondrial genome is PCR amplified using 46 pairs of overlapping primers. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. Results of molecular analysis must interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Detection**

Detection is related to the specific condition suspected (refer to the test descriptions for the recognized conditions listed above). Since in general, sequence analysis does not detect low level mutant heteroplasmy. Common mutations must be ruled out before the whole genome sequence is analyzed.

**Specimen Requirements**

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**Type: Whole Blood**

**Specimen Requirements:**

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Related Tests**

- Testing for Mitochondrial Genome Deletions is available by Southern blot analysis (ML) for common deletions associated with Kearns-Sayre syndrome (KSS), Pearson syndrome, Chronic Progressive External Ophthalmoplegia (CPEO) and other mitochondrial conditions.
- PCR amplification and restriction enzyme fragment analysis is available to test for Leigh syndrome (QD), Myoclonic epilepsy with ragged-red fibers (OH), and Leber hereditary optic neuropathy (QC).
- Testing for MELAS (Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) (QA) is available using sequence analysis of the MTTL1 gene and an allele-specific extension assay.
- Testing for Retinitis Pigmentosa and Ataxia (NARP) (QK) is available by PCR amplification with restriction enzyme fragment analysis and an allele-specific extension assay.
- Urine organic acid (OA) with lactic acid and pyruvic acid, and plasma acylcarnitine analysis (AR) may be considered for evaluation of specific mitochondrial disorders.
- Known mutation analysis (KM) is available to family members if mutation is identified in the proband by sequencing.